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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Wolfgang HEIL et al. : Group Art Unit: Unknown

Serial No.: 09/757,688 : Examiner: Unassigned

Filed: January 11, 2001 :

For: DROSPIRENONE FOR HORMONE REPLACEMENT THERAPY

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Please amend the above-identified application as follows:

In the Claims:

Cancel claims 1-76 in their entirety and insert the following new claims 77-132:

--77. A pharmaceutical composition comprising

as a first active agent, an estrogen (or naturally or synthetic derivative thereof) in sufficient amounts to treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women, and

as a second active agent, 6 ,7 ;15 ;16 -dimethylene-3-oxo-17 -preg-4-ene-21,17-carbolactone (drospirenone) in sufficient amounts to protect the endometrium from the adverse effects of estrogen,

together with a pharmaceutically acceptable excipient or carrier.

78. A composition according to claim 77, wherein the deficient levels of estrogen are caused by natural menopause, peri-menopause, post-menopause, hypogonadism, castration or primary ovarian failure.

79. A composition according to claim 77, wherein the diseases, disorders and symptoms are selected from the group comprising including hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition and osteoporosis.

80. A composition according to claim 79, wherein the diseases, disorders and symptoms are selected from the group comprising including hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, urogenital atrophy, atrophy of the breasts and osteoporosis.

81. A composition according to claim 77, wherein the estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, ethinyl estradiol, estrone, estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17 -estradiol sulfate, 17 -estradiol sulfate, equilin sulfate, 17 -dihydroequilin sulfate, 17 -dihydroequilin sulfate, equilenin sulfate, 17 -dihydroequilenin sulfate and17 -dihydroequilenin sulfate or mixtures thereof.

82. A composition according to claim 81, wherein the estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof.

83. A composition according to claim 82, wherein the estrogen is estradiol.

84. A composition according to claim 77, wherein drospirenone (DRSP) is in micronized form.

85. A composition according to claim 81, wherein the estrogen is in micronized form.

86. A composition according to claim 77, wherein the dose of DRSP corresponds to 15 to 70 mg per cycle, such as 20 to 60 mg per cycle, particularly 40 to 60 mg per cycle.

87. A composition according to claim 77, wherein the amount of DRSP corresponds to a daily dose ranging from 0.25 to 10 mg, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5, 1 to 4, and 1.5 to 3.5 mg.

88. A composition according to claim 83, wherein the amount of estradiol corresponds to a daily dose ranging from 0.1 to 5 mg, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular 1, 2, or 3 mg.

89. A pharmaceutical composition comprising

as a first active agent estradiol in amounts corresponding to a daily dose of 1 to 3 mg to treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women,

and as a second active agent 6 ,7 ;15 ;16 -dimethylene-3-oxo-17 -preg-4-ene-21,17-carbolactone (drospirenone) in amounts corresponding to a daily dose of 1 to 3.5 mg to protect the endometrium from the adverse effects of estrogen,
together with a pharmaceutically acceptable excipient or carrier.

90. A method of treating and preventing diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women comprising administering estrogen in sufficient amounts to alleviate said diseases, disorders and symptoms and drospirenone in sufficient amounts to protect the endometrium from adverse effects of estrogen.

91. A method according to claim 90, wherein the deficient levels of estrogen are caused by natural menopause, peri-menopause, post-menopause, hypogonadism, castration or primary ovarian failure.

92. A method according to claim 90, wherein the diseases, disorders and symptoms are selected from the group comprising including hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor

concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition or for the prevention or management of osteoporosis.

93. A method according to claim 92, wherein the diseases, disorders and symptoms are selected from the group comprising including hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, urogenital atrophy, atrophy of the breasts or for the prevention or management of osteoporosis.

94. A method according to claim 90, wherein the estrogen is selected from the group consisting of estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, ethinyl estradiol, estrone, estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17 -estradiol sulfate, 17 -estradiol sulfate, equilin sulfate, 17 -dihydroequilin sulfate, 17 -dihydroequilin sulfate, equilenin sulfate, 17 -dihydroequilenin sulfate and17 -dihydroequilenin sulfate or mixtures thereof.

95. A method according to claim 94, wherein the estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof.

96. A method according to claim 95, wherein the estrogen is estradiol.

97. A method according to claim 90, wherein drospirenone (DRSP) is in micronized form.

98. A method according to claim 90, wherein the estrogen is in micronized form.

99. A method according to claim 90, wherein the estradiol is in micronized form.

100. A method according to claim 90, wherein the dose of drospirenone corresponds to 15 to 70 mg per cycle, such as 20 to 60 mg per cycle, particularly 40 to 60 mg per cycle.

101. A method according to claim 90, wherein the amount of drospirenone corresponds to a daily dose ranging from 0.25 to 10 mg, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5, 1 to 4, and 1.5 to 3.5 mg.

102. A method according to claim 96, wherein the amount of estradiol corresponds to a daily dose ranging from 0.1 to 5 mg, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular 1, 2 or 3 mg.

103. A method according to claim 96 comprising administering estradiol in amounts corresponding to daily doses of 1 to 3 mg and drospirenone in amounts corresponding to daily doses of 1 to 3.5 mg.

104. A method according claim 90, comprising
administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg; and
administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and
administering for 4 to 8 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.25 to 5 mg.

105. A method according to claim 90, comprising
administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg; and
administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and
administering for 4 to 8 days a daily dosage unit comprising of a placebo or blank.

106. A method according to claim 90, comprising
administering for at least 21 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and
administering for no more than 7 days a daily dosage unit comprising of a placebo or blank.

107. A method according to claim 90, comprising
administering for at least 21 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and
administering for no more than 7 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg.

108. A method according to claim 90, comprising
administering for 21 to 28 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg.

109. A method according to claim 90, wherein the estrogen is administered continuously.

110. A method according to claim 90, wherein the estrogen and drospirenone are administered continuously.

111. A method according to claim 90, wherein the estrogen is administered continuously and drospirenone is administered sequentially.

112. A method according to claim 111, wherein the estrogen dosage is lower for the 1 to 7 days immediately following said sequential administration of drospirenone.

113. A method according to claim 90, wherein estrogen is administered continuously and drospirenone is administered in an interrupted manner.

114. A method according to claim 113, wherein estrogen is administered continuously for 21 to 30 days and drospirenone is administered in a 3-day-on-3-day-off cycle.

115. A method according to claim 114, wherein drospirenone is administered on days 4 through 6, 10 through 12, 16 through 18, 22 through 24, and 28 through 30.

116. A method according to claim 90, wherein the estrogen and the drospirenone are each administered sequentially with a treatment-free interval.

117. A method according to claim 90, comprising
administering for 20 to 24 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg,
and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 days, and
administering for 4 to 8 days a daily dosage unit comprising no active ingredient.

118. A method according to claim 90, comprising
administering for 20 to 24 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg, and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 day, and
administering for 4 to 8 days a daily dosage of unit comprising estradiol in amounts less than daily dosage unit taken for said 20 to 24 day administration of estradiol.

119. A method according to claim 90, comprising
administering for 20 to 24 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg,
and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 day, and
not administering any dosage units for 4 to 8 days.

120. A method according to claim 90, wherein the estrogen and/or drospirenone are administered in oral formulation, from a patch, from an implant or combinations thereof.

121. A method according to claim 120, wherein the estrogen and/or drospirenone are administered in oral formulation.

122. A method according to claim 104, wherein the daily dosage units are administered for 1 to 12, preferably 2 to 8, such as 2, 3, 4 5, 6, 7, and 8 multiples of 28 days.

123. A multi-phased pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of at least 21 days wherein said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg.

124. A multi-phased pharmaceutical preparation according to claim 123 consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 28 days.

125. A multi-phased pharmaceutical preparation according to claim 124 consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 28 days,
wherein at least 21 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and
no more than 7 said dosage units comprise a placebo or a blank.

126. A multi-phased pharmaceutical preparation according to claim 124, wherein
at least 21 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and
no more than 7 said dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg.

127. A multi-phased pharmaceutical preparation according to claim 124, wherein
at least 10 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg; and
at least 10 said daily dosage units comprises a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and
no more than 8 of said daily dosage units comprise a placebo or blank.

128. A multi-phased pharmaceutical preparation according to claim 124, wherein
at least 10 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg; and
at least 10 said daily dosage units comprises a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and
no more than 8 of said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg.

129. A multi-phased pharmaceutical preparation according to claim 123, consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 21 to 30 consecutive days,
wherein 10 to 15 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and

130. A preparation according to claim 123, wherein the number of daily dosage units is at least 21 or a multiple of 21 such as 2 to 12, particularly 2 to 8, such as 2 to 6.

131. A preparation according to claim 123, wherein the number of daily dosage units is 28 or a multiple of 28 such as 2 to 12, particularly 2 to 8 such as 2 to 6.

132. A preparation according to claim 123, wherein said daily dosage units comprise estradiol and/or drospirenone in micronized form or sprayed from a solution onto particles of inert carrier.--

REMARKS

This application is a non-provisional claiming benefit of a provisional application which, in turn, was converted from non-provisional, previously application serial number 09/484,026. Attached is a PTO form 1449 listing all of the references of record during that previous prosecution. Since copies of these references are available to the examiner from 09/484,026, copies are not necessary in accordance with the MPEP. However, should the examiner desire copies of any references, the undersigned will be happy to comply.

Respectfully submitted,

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